THE CALORIMETER AS THE INTERPRETER OF THE LIFE PROCESSES[1]

Shortly after the outbreak of the present war a scientific commission in Berlin reported that the quantity of energy units required during a year by 68,000,000 inhabitants in Germany amounted to about 57 thousand million calories, and that under changed conditions of dietary habits 81 thousand million calories would be available. In accordance with the requirements of the crisis the habits of the people were changed.

Our own Commission for Relief in Belgium forwarded food on the basis of the knowledge that 1,000 calories in cornmeal cost 11 mills, in wheat 14 mills, in rice 18 mills, in wheat flour 20 mills, in beans 29 mills, and in pork "fat backs" 28 mills.

All this was the world's recognition of the need of fuel for the life processes in human beings.

Rubner's work has made it possible to picture the energy liberated in various forms of living things. Thus Rubner estimates that a horse requires 11 calories per kilogram per day in order to maintain the normal life processes and for the fulfilment of the same necessities a man requires 30 calories per kilogram of body weight, a newborn mouse weighing one gram requires 654 calories per kilogram while a yeast cell weighing 0.000,000,000,5 gr. produces 1,743 calories per kilogram of substance, this also being the heat produced by a kilogram of diphtheria bacilli. The energy production in these lower forms of life was measured by determining the rise in temperature of the medium in which they lived when this was confined within the limits of a Dewar flask. The heat production of a kilogram of yeast thus measured was three fold that found for the same unit of mass in a newborn mouse, 58 times that of a man and 157 times that of a horse.

Although these values appear to be extremely variable, there is one unit of measurement which in mammalia is quite constant and that is the heat production per square meter of surface. Bergmann, in 1848, was the first to advance this hypothesis and a year later the French observers Regnault and Rieset stated that the heat production of sparrows per unit of weight was ten fold that of fowls, a phenomenon which they asserted was due to the fact that the smaller animals present a relatively larger surface to the surrounding air and thereby experience a considerable chilling, with the consequent generation of sufficient heat to maintain the normal body temperature. In 1883, Rubner published calculations which showed that the heat production of mammalia of various shapes and sizes was the same per square meter of surface. Figures are given such as 1,042 calories for man, 1,039 for the dog and 1,122 calories for the new-born mouse per square meter of surface during periods of 24 hours when the temperature of the environment is 15° C. and when moderate voluntary movements are permitted.

Further analysis showed Rubner that this evenness of heat production per unit of body surface was not due to any relation between the area of body surface and the area of cell surface within the organism. There are in one kilogram of body weight of man 150.2 square meters of such surface and each square meter of cell surface produces 0.2 calories per day. In the new-born mouse each square meter of cell surface produces eleven times this amount or 2.2 calories. It is of interest, also, to note that a kilogram of yeast cells presents a surface area of 600 square meters and at a temperature of 38°, or that at which mammalian cells exist, 1.25 calories per

[1] Read at the New York meeting of the National Academy of Sciences, November 16, 1915.

square meter of surface are produced in 24 hours, 8.34 grams of cane sugar undergoing inversion and fermentation during that interval. This reaction is independent of the strength of the sugar solution within the wide limits of 2.5 to 20 per cent. If the strength of the solution be at the maximum of normal reaction, or twenty per cent., the quantity of sugar utilized in twenty-four hours would be contained in a film 4/100 of a millimeter in thickness surrounding the cells. A like analysis shows that in man whose cells are bathed in a medium containing 0.1 per cent. of sugar the quantity necessary for the support of life during one day would be contained in a layer which if spread around the cell would be 5/100 of a millimeter in thickness.

From the calculation of the energy requirement in the food for the life of a nation to the energy liberated by a yeast cell in its simple resolution of sugar into alcohol and carbon dioxide is indeed a far cry, except as showing that the energy doctrine, as enunciated by Rubner, unites the world of living things.

In 1912 I calculated that the heat production of three quiet and sleeping dogs was 759, 748 and 746 calories per square meter of surface at an environmental temperature of 26°, that a dwarf produced 775 calories per square meter of surface, and that four out of five sleeping men investigated by Benedict showed an average heat production of 789 calories per unit of area. Only in the sleeping infant 7 months old investigated by Howland, did the metabolism appear out of the ordinary and reached a level of 1,100 calories, and this factor was specifically pointed out as indicating a higher metabolism in the youthful protoplasm than is present in the adult.

When the Russell Sage Institute of Pathology constructed in Bellevue Hospital an Atwater-Rosa calorimeter copied in the main after the successful models of Benedict, it became absolutely essential that some criterion of normal metabolism be established, as a basis from which one could estimate whether the metabolism of a patient under investigation was higher or lower than the normal. The severe criticisms of Benedict upon the method of estimating heat production from the unit of surface led to a very careful review of all the evidence and to new experiments. Du Bois, who took up this work, has used an accurate and ingenious method with which he has been able to actually measure the surface area of normal men. He and Mr. Delafield Du Bois have discovered that the formula heretofore used for estimating the surface area in man showed an average inaccuracy of 16 per cent. and a maximal variation from the normal of 36 per cent., this being found in very fat individuals. A new formula has been evolved which gives an average variation of $\pm$ 1.5 per cent. and a maximal variation of $\pm$ 5 per cent. Using the older formula of Meeh, the heat production per square meter of surface is 833 calories during 24 hours, but using the more accurate formula of Du Bois that rises sixteen per cent. to 953 calories. In normal adults of various shapes and sizes this is the *basal metabolism* as measured when the individual is resting and before the administration of food in the morning. The variation from this standard does not exceed 10 per cent. in 90 per cent. of the cases. The maximal variation is 15 per cent.

The critical studies of F. G. Benedict have been especially helpful in stimulating the reconsideration of all the data and methods in relation to this subject. Benedict is in agreement with Carl Voit when he concludes that the mass of active proto-

plasmic tissue determines the height of the metabolism. However, in the search for a standard upon which to calculate what would be the normal heat production of a man suffering from disease it is obviously impossible to measure the mass of active protoplasmic tissue. It is, therefore, most fortunate that the unit of surface area eliminates the same amount of heat in the normal adult within ten per cent. of a determined average.

The reason for this is not clear, but the fact is established. It is known that a regulating mechanism maintains the body temperature at a fixed point, though the reason for this is also undetermined.

The figures given hold true for the adult but are subject to variations due to age.

Murlin has pointed out that the newborn baby has a distinctly lower metabolism than normal and that this rapidly rises during the first year to a standard above the normal. It should be remembered in the first place, that the newly born may be considered in the light of an internal organ which has been protected from external stimuli. This is indicated by the work of Murlin upon the pregnant dog and from that of Murlin and Carpenter upon the human mother. The increase in heat production during the first months of the infant's life may be due to the union of the muscles with medullated nerve fibers. Furthermore, one finds on analysis that there is 24 per cent. of muscle tissue in the newly born baby as against 42 per cent. or nearly double that quantity in the adult. These proportions are reversed as regards glandular tissue, there being 47 per cent. of this tissue in the newborn and only 24 per cent. in the adult. It is this preponderance of glandular tissue in early life that may be the cause of the prevalence of the higher metabolism during the early period of growth. Du Bois has found that in a number of boys just before puberty the heat production is 25 per cent. above the normal and it is interesting to query whether this be due to glandular activity.

With the approach of old age the metabolism falls about ten per cent.; there is no longer quite the same intensity of oxidation as at the height of a man's virility.

In conditions of disease, as in those of health, the same materials, such as protein, fat and carbohydrate are oxidized and in the normal fashion, and they produce heat after the normal manner. The disease of diabetes presents a striking exception, as sugar may here remain unoxidized. In general, one may say that the intensity of the metabolism processes are little affected in many diseased conditions. In diabetes the heat production does not rise appreciably above the normal. The calorimeter in the hands of Du Bois and his fellow worker has shown that in severe anemias and in heart disease involving dyspnea, the heat production may increase. This is very probably due to the stimulus of lactic acid, a similar phenomenon being witnessed in a dog poisoned with phosphorus. In a typical fever such as typhoid the heat production may increase between 40 to 50 per cent. and in severe cases of exophthalmic goiter it rises to between 75 to 100 per cent. above the normal. It is fortunate that the ingestion of food which in the normal individual causes an increase in heat production, does not abnormally stimulate the fires of metabolism in these patients already suffering from intensified oxidation processes.

The inner process of heat production involves the interplay between the living cells of the body and the nutrient constituents of the fluids which bathe them. It has been known since the time of Lavoisier that the ingestion of food results in an increase in metabolism. In the presence of

abundant food the cells produce heat in increasing measure. Thus, after giving meat alone in large quantity to a quietly resting dog the heat production may be double that of the normal basal metabolism. The constituent amino-acids of protein are relieved of their NH_2 groups and the denitrogenized remainders are utilized for heat production, any excess being converted into glucose and retained in the organism as glycogen. The great rise in heat production is in large measure due to the direct chemical stimulation of the cells through the metabolism products of certain amino-acids. The proof of this lies in the fact that if glycocoll or alanine be given to the diabetic dog the heat production is largely increased, although these substances are not oxidized and there is therefore no evolution of heat from them, for they are converted into glucose and urea which appear in the urine. When the same method is applied to the study of the sugars, it fails to support the idea that the intermediary products of sugar metabolism directly stimulate the cells to a higher heat production. Thus, fructose administered to a diabetic dog caused no increase in heat production, although it underwent chemical change, for it was found as glucose in the urine. Since all the evidence regarding this reaction points to a preliminary cleavage of fructose which contains six carbon atoms into two molecules each containing three atoms of carbon and to the subsequent synthesis of these molecules into glucose, one may reason that the preliminary cleavage products of carbohydrate metabolism are not direct stimuli to protoplasm, as are those of amino-acids like glycocoll and alanine, but that normally the mere presence of a large number of metabolites of sugar results in their oxidation in increased measure.

Rubner has shown that when the yeast cell is bathed in a solution of sugar and peptone the protein is used for growth or cell repair only, while alcoholic fermentation furnishes the energy, and as before stated the quantity of this energy is independent of the strength of the solution. So also in a mammal such as the dog, if one give 50, 70 or 100 grams of glucose, the energy production increases in all cases to a level of about 30 per cent. above the normal. It appears that the cells by a process called "self-regulation" use the fragments of broken glucose up to a certain limit which is not transcended. Any excess of these fragments is converted into glycogen or into fat, a small quantity of energy being absorbed in the first process and a small quantity being liberated in the second. The result of this is that beyond a certain limit of carbohydrate plethora, the heat production in the dog scarcely rises, and this is analogous to the behavior of the yeast cell towards its nutritive environment.

The study of the intermediary metabolism upon which the total heat production of an animal is based, furnishes a fascinating field for the scientist, and it is also evident that the study of the fuel requirement of the human individual in health and in disease presents many problems of importance for the general welfare of the community at large.

Graham Lusk

OBSTACLES TO RESEARCH[1]

The duty of the university to investigate the unknown as well as to teach the known is clearly evident. In the performance of this duty, the importance of research work is emphasized in many ways. Promise of productive scholarship is a leading qualification demanded in selecting members of the faculty. Encouragement and facilities for original

[1] An address delivered before the Minnesota Chapter of the Sigma Xi Society, October 21, 1915.